pearing between the 6-methyl and 4-carbonyl groups. The epimerization through routes A or B should furthermore be accompanied by deuteration of the C-9 methylene, in deuteration experiments, because of the imine–enamine tautomerism.[12] In fact, epimerization does occur also with the 6-methyl derivatives **2b** and **3b**, and deuteration takes place at C-3 but not at C-9 on addition of trifluoroacetic acid in the presence of deuterium oxide. We therefore conclude that the epimerization of these derivatives (**2** and **3**) proceeds via oxo–enol tautomerism (route C).

Experimental Section

Infrared (IR) spectra were obtained with KBr disks on a Zeiss UR-20 spectrophotometer. The ^1H, ^{13}C, and ^{15}N NMR spectra were recorded of samples in $CDCl_3$ in the PFT mode (16K data points for the FID) at ambient temperature with an internal deuterium lock at 99.6, 25.0, and 10.04 MHz by using a JEOL FX-100 multinuclear spectrometer. The ^1H and ^{13}C chemical shifts were determined on the δ scale by using tetramethylsilane (δ 0) as an internal standard. The concentration of ^1H NMR samples was about 0.1 mol/L, and that of the ^{13}C and ^{15}N samples was about 0.5–1.0 mol/L. ^{15}N chemical shifts were measured at natural abundance levels, were determined relative to the signal of external aqueous $K^{15}NO_3$, and then were converted to external neat nitromethane ($\delta_{CH_3NO_2} = 0$). Typical acquisition parameters included a spectral width of 5000 Hz, a flip angle of 30°, and pulse delays up to 5 s.

All GLC analyses were accomplished with a Hewlett-Packard 5830 A instrument on SP 2100 in a glass capillary column (10 m) with argon (2 mL/min) as the carrier gas and a temperature program (10 °C/min) from 150 to 250 °C. Mass spectral analyses were carried out with a JEOL B-300 spectrometer fitted with a JMA 2000 β system.

The epimerization experiments were carried out in 0.1 M ethanolic solution, the product ratio was determined by GLC analysis in base form.

Melting points were measured in capillaries and are uncorrected.

Hydrogenation. Tetrahydropyridopyrimidine (10 mmol) in acetic acid (10 mL) was hydrogenated over PtO_2 (60 mg) at 30 °C under a pressure of 62 atm (about 24 h). After the catalyst was filtered out, the acetic acid was removed under reduced pressure. The residue was dissolved in methylene chloride (5 mL) and washed with 3% $NaHCO_3$ solution (50 mL). The aqueous phase was extracted three times with methylene chloride (1 mL each), and the combined organic solutions were dried (Na_2SO_4) and evaporated.

Separation of the Diastereomers. The product of the hydrogenation of **1a** (2.08 g, mixture of **2a** and **3a**) was recrystallized first from 5 volumes and then twice from 10 volumes of toluene at 50 °C to yield **2a**: 0.29 g; mp 146 °C; IR ν_{CO} 1614 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.37; H, 7.95; N, 12.11.

The toluene mother liquor was concentrated to give a crystalline fraction (mp 80–86 °C) which was recrystallized twice from an equal volume of toluene to yield **3a**: 0.6 g; mp 87 °C; IR ν_{CO} 1625 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.12; H, 7.83; N, 12.35.

The product of the hydrogenation of **1b** (2.34 g, mixture of **2b** and **3b**) was dissolved in ethyl acetate (14 mL) and left for 2 days at 15 °C to crystallize. The crystals (0.8 g; mp 161 °C) were treated with dry hydrochloric acid in ethanol to give the hydrochloride salt. The latter was recrystallized twice from ethanol to give the hydrochloride of **2b**: 0.5 g; mp 234–237 °C; IR ν_{CO} 1632 cm^{-1}. The base was liberated ($NaHCO_3$, CH_2Cl_2) and recrystallized from toluene (6 mL) at 60 °C to yield **2b**: 0.37 g; mp 176 °C; IR ν_{CO} 1629 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 63.88; H, 7.54; N, 10.21.

The ethyl acetate filtrate was evaporated, and the oil was dissolved in an ethanolic solution of hydrogen chloride. The solution was seeded with the hydrochloride of **2b** and the separated **2b** hydrochloride salt filtered off after 1 day. The mother liquor was evaporated to half of its volume and diluted with an equal volume of ethyl acetate, and the precipitated crystals were filtered off to yield the hydrochloride of **3b**: 0.7 g; mp 183–187 °C; purity 95% (on the basis of GC analysis); IR ν_{CO} 1657 cm^{-1}. The base was liberated as above and dissolved in toluene (1.7 mL) at 30 °C, and the solution was diluted with hexane (2 mL) and left to crystallize at 10 °C to give **3b**: 0.41 g; mp 98 °C; IR ν_{CO} 1624 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 63.90; H, 7.70; N, 10.18.

6-Methylperhydropyrido[1,2-*a*]pyrimidin-4-one (4). To 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[4d] (1.69 g) in water (20 mL) was added dropwise at 10 °C a solution of $NaBH_4$ (1.2 g) in water (10 mL) over 20 min. The solution was stirred for 2 h at 10 °C, and it was made acidic (pH 2–3) with 1:1 HCl. The pH was then adjusted to 8 with 10% aqueous Na_2CO_3. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the organic layer was dried ($MgSO_4$) and evaporated. The residue was distillated to give perhydropyridopyrimidinone **4**: 0.9 g; bp 135–140 °C (1 mmHg); HCl salt, mp 210 °C (EtOH).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.97; H, 9.71; N, 16.82.

Acknowledgment. We are indebted to Mr. B. Podányi for technical assistance.

Registry No. 1a, 39080-63-2; **1b**, 54672-35-4; **2a**, 83077-47-8; **2b**, 83077-48-9; **2b**·HCl, 83148-38-3; **3a**, 83077-49-0; **3b**, 83148-37-2; **3b**·HCl, 83198-16-7; **4**, 83077-50-3; **4**·HCl, 83077-51-4; 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 32092-29-8.

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Conformational Analysis. 44. 1,1,2-Trimethylcyclohexane[1]

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In a previous joint study with a group of Soviet investigators,[2,3] we had pointed out that the position of conformational equilibrium in 1-X-2,2-dimethylcyclohexanes (Scheme I, A ⇄ B) was almost the same as the position of the corresponding equilibrium for cyclohexyl-X (Scheme I, C ⇄ D). In essence, this means that, surprisingly, the extra CH_3/X gauche interaction in B (compared to A) does not seem to affect the conformational equilibrium of X to any palpable degree (<0.1 kcal/mol).

The substituents X in the previous[2] investigation were OCH_3, $OCOCH_3$, $OSi(CH_3)_3$, and OH, and the position of conformational equilibrium was based on the magnitude of the coupling constant of the C*H*X proton with vicinal protons of the ring or on the half-width of the C*H*X signal. This is not a highly accurate means of assessing $\Delta G°$; in addition the substituents investigated have rotational conformational inhomogeneity, are polar ($\Delta G°$ is somewhat dependent on solvent[2]), and, in the case of OH, are subject to hydrogen bonding.[4] We felt it would be worthwhile to investigate the case where X = CH_3, a nonpolar group, and

(1) Paper 43: Eliel, E. L.; Manoharan, M.; Hodgson, D. J.; Eggleston, D. S. *J. Org. Chem.*, in press.

(2) Mursakulov, I. G.; Ramazanov, E. A.; Guseinov, M. M.; Zefirov, N. S.; Samoshin, V. V.; Eliel, E. L. *Tetrahedron* **1980**, *36*, 1885.

(3) See also Mursakulov, I. G.; Guseinov, M. M.; Kasumov, N. K.; Zefirov, N. S.; Samoshin, V. V.; Chalenko, E. G. *Tetrahedron*, in press.

(4) Cf. Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487.

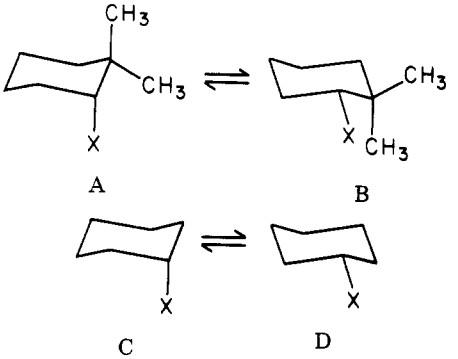
0022-3263/82/1947-4783$01.25/0

Table I. ^{13}C NMR Signals of Compounds 1 and 2[a,b]

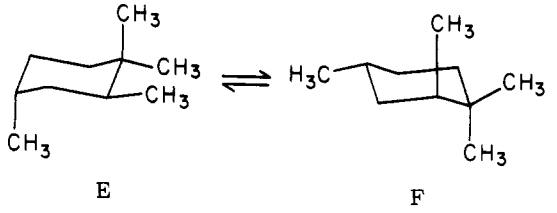
entry	compd	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	CH_3(1)	CH_3(1)	CH_3(2)	CH_3(4)
1	1[c]	32.7_5 (33.2)	40.9_7 (42.4)	40.4_2 (40.8)	35.2_5 (33.0)	31.6_3 (32.3)	42.2_3 (41.8)	18.5_4[d] (19.7)	30.5_4[e] (31.1)	16.4_1 (16.9)	22.7_1 (23.3)
2	2[f]	32.8_5 (32.9_8)	37.1_3 (37.4_4)	38.3_4 (38.3_7)	27.2_0 (26.8_5)	30.2_8 (29.8_0)	35.0_9 (35.0_2)	24.9_9 (25.0_4)	28.9_4 (28.7_6)	16.2_9 (16.4_1)	21.0_9 (21.1_5)
3	2 (E)[g]	32.0_9 (31.3)	36.5_4 (37.0)	38.3_7 (37.1)	27.7_2 (28.5)	28.0_5 (28.6)	34.2_8 (36.4)	17.9_9[d] (19.7)	30.7_8[e] (31.1)	16.6_2 (16.9)	18.3_8 (18.5)
4	2 (F)[g]	33.6_0 (32.7)	38.0_7 (38.4)	38.3_7 (37.3)	26.2_4 (27.5)	31.1_8 (32.0)	35.5_4 (35.0)	27.3_3[d] (25.5)	29.9_9[e] (31.1)	16.2_6 (<17)	23.1_0 (23.3)

[a] Shifts in parts per million from Me_4Si. [b] The values in parentheses are calculated shifts; see text. [c] In $CDCl_3$ at 25 °C. [d] Axial methyl. [e] Equatorial methyl. [f] In CD_2Cl_2 at 25 °C. [g] In CD_2Cl_2 at −90 °C.

Scheme I



Scheme II



to assess $\Delta G°$ by the accurate method of low-temperature ^{13}C NMR spectroscopy. The results, reported in the sequel, bear out the earlier ones;[2] there is but a small (ca. 0.2 kcal/mol) vicinal interaction slightly disfavoring B (vs. A) relative to D (vs. C).

Results and Discussion

Anticipating that for X = CH_3 (in analogy with the earlier cases studied[2]) the equilibrium in Scheme I, A ⇄ B, would be too far on the side of B to be easily and accurately measurable, we chose a "counterpoise" method[5] in which the 2-methyl group in 1,1,2-trimethylcyclohexane is balanced by a methyl group at C(4); the compound required for study is, thus, *trans*-1,1,2,4-tetramethylcyclohexane (Scheme II). This compound was synthesized from the known 4,4-dimethylcyclohex-2-en-1-one by 1,4 addition of methylmagnesium iodide in the presence of copper iodide,[6] followed by a Wittig reaction with methylenetriphenylphosphorane[7] and catalytic hydrogenation (Scheme III). The product was a mixture of cis (1) and trans (2) isomers (with the former predominating), which were separated by gas chromatography.

The room-temperature ^{13}C NMR spectra of 1 and 2 are recorded in Table I. Signal assignments were made by a combination of off-resonance decoupling (sford) and parametric prediction of shifts based on the known[8,9] chemical shifts of 1,1-dimethylcyclohexane, 1,1,2-trimethylcyclohexane, and *cis*- and *trans*-1,3-dimethylcyclohexane. Predictions for 1 on this basis were straightforward, and the anticipated signal positions agreed well with the experimental ones. In the case of 2 it was necessary to make predictions for both E and F (Scheme II) separately. This was done by employing known[8,9] substitution parameters for equatorial and axial methyl groups and (in the case of F) by making the additional assumption that the value of the vicinal (a,a) parameter was zero. Finally, the predicted spectra of E and F were averaged on the crude a priori assumption that E and F existed in 1:1 proportions at equilibrium at room temperature.

Table II. Calculated Equilibrium Constants (F/E)

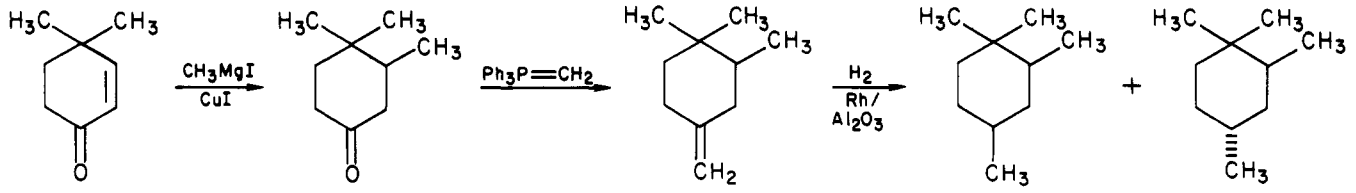
	rel area F	rel area E	K	$-\Delta G°$, kcal/mol
C(1)	97	34	2.85[a]	0.38
C(2)	93	60	1.55	0.16
C(3)	117	117	*b*	*b*
C(4)	85	53	1.60	0.17
C(5)	115	52	2.21	0.29
C(6)	53	41	1.29	0.09
CH_3(1)	109	51	2.13	0.28
CH_3(1)	106	52	2.04	0.26
CH_3(2)	104	62	1.68	0.19
CH_3(4)	92	47	1.95	0.24
average			1.81 ± 0.32	0.21 ± 0.07[c]

[a] Omitted in average. [b] Signals not resolved. [c] Calculated from averaged K.

The low-temperature spectrum of 2 at −90 °C shows two sets of signals due to E and F (Scheme II) whose positions are summarized in Table I (lines 3 and 4). Because all peaks occur in a relatively narrow region of the spectrum (15–40 ppm), assignments were relatively difficult. We used three principles for this assignment: (1) the assigned shifts should be close to the frequencies calculated as explained above; (2) the set of the larger signals should be consistently assigned to one conformational isomer and the set of the smaller ones to the other; (3) the average shift of the two signals (using the finally determined $\Delta G°$) assigned to a given position should be close to the room-temperature value of the signal assigned to that position. The first criterion is documented by the parenthesized values in Table I, the second one by the integrated areas of the signals summarized in Table II, and the third by

(5) For a recent example and references, see Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.
(6) Eliel, E. L.; Hutchins, R. O.; Knoeber, M. *Org. Synth.* **1970**, *50*, 38.
(7) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
(8) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 6612. *Ibid.* **1972**, *94*, 5318.
(9) For a convenient summary of the data, see Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 64.

Scheme III



a comparison of calculated and experimental room-temperature signal positions shown (in parentheses) in Table I. (It must be taken into account that shifts can easily fluctuate by 0.3–0.5 ppm when the temperature is changed by 120 °C.)

Although we cannot be certain that the low-temperature assignments are all correct, they give rise to a reasonably consistent equilibrium constant (F/E) of 1.81 ± 0.32, corresponding to a $-\Delta G°$ of 0.21 ± 0.07 kcal/mol at −90 °C. The corresponding equilibrium constant at room temperature, assuming $\Delta S° = 0$, is 1.42 (58.7% F, 41.3% E), and it is this constant that was used in the above-mentioned calculations of room-temperature shifts.

The conclusion, then, is that although F is favored over E by 0.21 kcal/mol, this is much less than the value of the extra Me/Me gauche interaction expected in E as compared to F (0.6–0.87 kcal/mol). On this basis, $-\Delta G°$ for the conformational equilibrium A ⇄ B, X = Me, shown in Scheme II would be 1.74 (the value for C ⇄ D, X = Me)[10] minus 0.21 or 1.53 kcal/mol. This value may have to be slightly lowered (perhaps by 0.1 kcal/mol) if one takes into account that $-\Delta G°$ for 4,4-dimethylcyclohexyl-X is slightly lower than that for cyclohexyl-X itself[11] and that the actual reference point for the 2-Me in Scheme II is the 1,1,4-trimethylcyclohexane system. However, the conclusion that the extra Me/Me gauche interaction in E (Scheme II) is only between one-half and one-fourth of the expected value remains certain. The situation shown in Scheme I, A ⇄ B, X = CH_3, is thus analogous to that earlier reported[1] for X = OH, OAc, $OSiMe_3$, OMe.

In order to eliminate the possibility that a major entropy effect favoring E over F (Scheme II) might be responsible for the small measured $\Delta G°$, we repeated the equilibrium measurements at −110 and −75 °C. The $\Delta G°$ values at these temperatures, 0.20 ± 0.06 and 0.20 ± 0.08 kcal/mol, are not materially different from those at −90 °C; thus, there seems to be no major entropy difference between the conformers.

A possible reason for the unexpectedly small free energy difference between E and F is a destabilization in F, caused by the anti-diaxial methyl groups, to compensate for a destabilization in E, likely to be caused by the extra gauche Me/Me interaction. Ourisson's "reflex effect"[12] is a potential cause[13a] of this destabilization, but, if so, the geminal equatorial methyl group at C(1) must play an essential role, since no corresponding anomaly is seen in the a,a ⇌ e,e equilibrium of *trans*-1,2-dimethylcyclohexane.[13b]

Experimental Section

Proton NMR spectra were recorded on a Perkin-Elmer R24B (60 MHz), a Varian XL-100 (100 MHz), or a Bruker spectrospin WM-250 (250 MHz) spectrometer. Carbon-13 NMR spectra were recorded on the Bruker spectrospin WM-250 (62.89 MHz) instrument operated in the pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 10–15% solutions in $CDCl_3$ or CD_2Cl_2 with 2–5% Me_4Si as internal reference in 5-mm o.d. tubes. For the room-temperature spectra, the sweep width was 15 000 Hz, the acquisition time was 0.52 s, and there were 16K data points. For 1, the number of transients was 1000 and the pulse width was 0.5 μs; for 2, the number of transients was 4000 and the pulse width was 9 μs. At −110, −90, and −75 °C the sweep width was 5000 Hz, there were 16K data points, the acquisition time was 1.64 s, the number of transients was 1000, and the pulse width was 14 μs. Typical line widths were 2.1 Hz at −75 °C, 3.0 Hz at −90 °C, and 3.7 Hz at −110 °C. For area measurements, portions of spectra were expanded and recorded at a sweep width of 300 Hz. The individual peaks were electronically integrated, and the ratio of the heights of the integral tracings was taken as peak area ratios. Analytical gas–liquid partition chromatography was carried out in a Hewlett-Packard 5750 research chromatograph equipped with 12 ft × 0.125 in. 20% SE-30 on Chromosorb 80–100 mesh column and flame-ionization detector. Preparative GLC was performed in a Varian Aerograph Model 2700 equipped with the following column: 12 ft × 0.375 in., 30% SE-52 on 80–100 Chromosorb A.

4,4-Dimethylcyclohex-2-en-1-one. 4,4-Dimethylcyclohex-2-en-1-one was prepared according to the procedure reported by Bordwell and Wellman:[14] ^1H NMR ($CDCl_3$) δ 1.15 [s, 6 H, $(CH_3)_2$], 1.80 (m, 2 H, methylene at C-5), 2.40 (m, 2 H, methylene at C-6), 5.67–6.49 (AB spectrum, 4 lines, J_{AB} = 10.0 Hz, 2 H, vinyl protons).

3,4,4-Trimethylcyclohexanone. 3,4,4-Trimethylcyclohexanone was prepared from 4,4-dimethylcyclohex-2-en-1-one by a modification of a procedure described[6] for the 1,4 addition of methylmagnesium iodide in the presence of copper chloride. Methylmagnesium iodide was prepared by the addition of a solution of methyl iodide (68.27 g, 0.48 mol) in anhydrous ether (125 mL) to a suspension of magnesium (9.77 g, 0.40 mol) in anhydrous ether (25 mL) under nitrogen. The resulting solution of the Grignard reagent was cooled to 0–5 °C with an ice–salt bath, and dry copper(I) iodide (3.82 g, 0.02 moL) was added with stirring. The resulting mixture was kept at −5 to 0 °C while a solution of 4,4-dimethylcyclohex-2-en-1-one (25.00 g, 0.20 mol) in anhydrous ether (38 mL) was added, dropwise, over a period of 35 min. The reaction mixture was further stirred for 60 min at room temperature and then poured onto a mixture of 400 g of ice and 215 mL of 10% sulfuric acid. The ether layer was separated and the aqueous phase was extracted with ether (3 × 150 mL). The combined ether extracts were washed with saturated aqueous sodium thiosulfate (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated on the rotary evaporator to leave a residue, which, on distillation under reduced pressure, yielded 3,4,4-trimethylcyclohexanone: yield 22.03 g (78%): bp 61–64 °C (7 mm) [lit.[15] bp 80–81 °C (12 mm)]; ^1H NMR ($CDCl_3$) δ 0.91 (d, J_{HCCH} = 7.0 Hz, 3 H, CH_3 at C-3), 1.00 (s, 3 H, CH_3 at C-4), 1.04 (s, 3 H, CH_3 at C-4), 1.42–2.47 (complex multiplet, 7 H, ring protons).

3,4,4-Trimethyl-1-methylenecyclohexane. 3,4,4-Trimethyl-1-methylenecyclohexane was prepared from 3,4,4-trimethylcyclohexanone by a modification of the procedure described

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(11) Bailey, D. S.; Walder, J. A.; Lambert, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 177.
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(13) (a) A referee has suggested gear effects as a possible cause for stabilization of the conformer with the equatorial 2-methyl group. While we have no information on this point, ref 2 relates to groups (OCH_3, OAc, OH) where gear effects are unlikely to play a part. (b) Manoharan, M.; Eliel, E. L., unpublished observations.
(14) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1347.
(15) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin, Trans. 1.* **1973**, 529.

by Corey et al.[7] for a typical Wittig reaction. The methyltriphenylphosphonium bromide was obtained from the Aldrich Chemical Co. and was dried at 120 °C under vacuum overnight prior to use. The solvent (dimethyl sulfoxide) was dried over CaH_2 and distilled prior to use. To sodium hydride (0.066 mol as a 50% dispersion in mineral oil), which had been washed several times with small portions of pentane, was added 33 mL of dimethyl sulfoxide under nitrogen, and the mixture was heated at 75–80 °C with stirring for 45 min. The resulting solution was cooled in an ice–water bath and stirred, and a solution of methyltriphenylphosphonium bromide (23.60 g, 0.066 mol) in dimethyl sulfoxide (66 mL) was added dropwise with stirring over a period of 15 min. After an additional 15 min at room temperature, 3,4,4-trimethylcyclohexanone (10.00 g, 0.071 mol) was added to the ylide solution, and stirring was continued for 40 min. Distillation of the reaction mixture at 105 mm yielded a distillate, which was collected between 50 and 90 °C. The distillate was dissolved in pentane (30 mL) and washed with water (2 × 15 mL). The pentane layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure (100 mm) to leave a residue, which on passage through a preparative GLC column (12 ft × 0.375 in. 30% SE-52 on 80–100 Chromosorb A) at 100 °C yielded 1.00 g (10%) of 3,4,4-trimethyl-1-methylenecyclohexane: ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 7.0 Hz, 3 H, CH_3 at C-3), 0.84 (s, 3 H, CH_3 at C-4), 0.91 (s, 3 H, CH_3 at C-4), 0.98–2.21 (complex multiplet, 7 H, ring protons), 4.56 (partially resolved inner portion of AB, 2 H, $=CH_2$).

***cis*- and *trans*-1,1,2,4-Tetramethylcyclohexane (1 and 2).** Hydrogenation of 3,4,4-trimethyl-1-methylenecyclohexane (0.800 g, 0.006 mol) in methanol (20 mL) with 374 mg of 5% Rh on alumina catalyst at atmospheric pressure in a Parr hydrogenator was completed in 8 h. The mixture was filtered through a Celite bed in a disposable pipet. The filtrate was dissolved in pentane (30 mL), extracted with water (2 × 20 mL), and dried over anhydrous $MgSO_4$. Evaporation of the pentane at atmospheric pressure left a residue containing a mixture of 1 and 2: yield 580 mg (69%). The mixture was separated by preparative GLC on a 12 ft × 0.375 in., 30% SE-52 on 80–100 Chromosorb A, column at 90 °C. The cis isomer (60%) emerged first, followed by the trans isomer (40%): ^1H NMR ($CDCl_3$) (cis isomer, 1) δ 0.73 (s, 3 H, equatorial CH_3 at C-1), 0.78 (d, J_{HCCH} = 7.0 Hz, 3 H, CH_3 at C-2 or C-4), 0.87 (d, J_{HCCH} = 7.0 Hz, 3 H, CH_3 at C-4 or C-2), 0.88 (s, 3 H, axial CH_3 at C-1), 0.93–1.52 (complex multiplet, 8 H, ring protons); ^1H NMR (CD_2Cl_2) (trans isomer, 2) δ 0.79 (s, 3 H, equatorial CH_3 at C-1), 0.86 (d, J_{HCCH} = 6.9 Hz, 3 H, CH_3 at C-2 or C-4), 0.89 (d, J_{HCCH} = 6.9 Hz, 3 H, CH_3 at C-4 or C-2), 0.93 (s, 3 H, axial CH_3 at C-1), 1.07–1.76 (complex multiplet, 8 H, ring protons); ^{13}C NMR, see Table I. Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.54; H, 14.40 (for cis–trans mixture).

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Registry No. 1, 83152-08-3; 2, 83152-09-4; 3,4,4-trimethylcyclohexanone, 40441-35-8; 4,4-dimethylcyclohex-2-en-1-one, 1073-13-8; 1,1,2-trimethyl-4-methylenecyclohexane, 83159-78-8; $Ph_3P{=}CH_2$, 3487-44-3.

Chemistry of Ambergris. 1. A Short Synthesis of (±)-δ-Ambrinol

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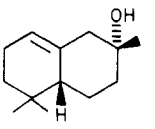
Introduction

Ambergris, a concretion formed in the intestinal tract of the blue sperm whale, has long been prized by perfumers for its unique fragrance properties. Faced with the possibility of the whales' extinction, many nations have prohibited their hunting and the importation of whale products. This has necessitated a search for synthetic ambergris compounds that may be used as substitutes in perfumery. Although α-ambrinol (1) is regarded as one



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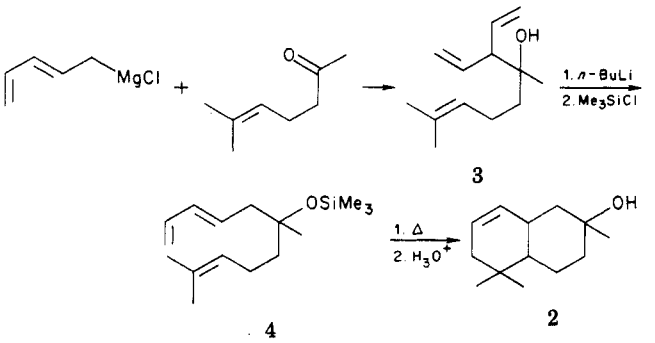
of the most important constituents of tincture of ambergris,[2] it has attracted very little synthetic attention.[3] The recent resurgence of interest in the intramolecular Diels–Alder reaction[4] prompts us to report a short synthesis of δ-ambrinol (2) from methylheptenone and pentadienylmagnesium chloride (Scheme I). Four stereoisomers of **2** were obtained, but only **2a** and **2b** have a strong ambergris odor. The assignment of stereochemistry to all four isomers necessitated an in-depth NMR study, which has demonstrated the advantages of combining ^{13}C NMR with high-field proton spectroscopy and lanthanide-induced shift techniques for stereochemical studies in hydroxydecalin systems.

Scheme I



Discussion

2,4-Pentadienylmagnesium chloride reacted smoothly with methylheptenone to give trienol **3** in 67% yield. The reaction of **3** with potassium hydride in tetrahydrofuran gave methylheptenone. However, rearrangement of the lithium alkoxide proceeded smoothly in refluxing tetrahydrofuran, providing, after quenching with chlorotrimethylsilane, the triene ether **4**.[5] The key intramolecular Diels–Alder cyclization was carried out at 220 °C in toluene to give, after hydrolysis and distillation, δ-ambrinol as a mixture of four stereoisomers, **2a–d** (ratio 5:30:10:2, re-

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